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Stimulation of motor tracts in motor neuron disease

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SUMMARY The muscle responses evoked by cortical and cervical stimulation in 11 patients with motor neuron disease were studied. The muscle potential in the abductor pollicis brevis, evoked by median nerve stimulation and the somatosensory potential evoked by wrist stimulation were also studied. In eight of 11 patients there was absence or increased central delay of the responses evoked by cortical stimulation. In four patients muscle responses on cervical stimulation and muscle action potentials on median nerve stimulation were also altered, indicating peripheral abnormalities. Somatosensory responses evoked by wrist stimulation were normal. Electrophysiological techniques are helpful in estimating the site of motor involvement in motor neuron disease.

In 1980 Merton and Morton[1] introduced percutaneous cortical stimulation with brief high voltage electrical shocks delivered by a low output stimulator. The stimulus produces contralateral muscle contraction, at a latency compatible with conduction in fast corticospinal axons. The same stimulus applied to the cervical region produces bilateral muscle contraction.[2] By combining the two sites of stimulation it is possible to calculate the central motor conduction delay.[2 3] Abnormalities in the central motor pathways have thus been demonstrated in patients with multiple sclerosis[4 5] and attributed to demyelination of corticospinal axons. In patients with Parkinson's[6] and Huntington's diseases[7] it has been proved that the corticomotoneuron connection is normal.

We have studied the muscle evoked potentials after cortical and cervical stimulation in patients with motor neuron disease and have also measured median nerve conduction and somatosensory potentials evoked by wrist stimulation.

Patients and methods

The study was performed in 11 patients aged 39–68 years (mean age 53) with motor neuron disease (amyotrophic lateral sclerosis) and in 20 normal controls selected from a group of 50, on the basis of the age (aged 35–64 years, mean 50) and height, including the authors. Informed consent was obtained and the study was approved by the local ethical committee.

Case selection was based on the following criteria: (1) progressive muscular weakness and atrophy, (2) fasciculations of affected muscles, (3) clinical signs of pyramidal tract lesion, (4) absence of sensory signs, sphincter abnormalities and dementia, (5) normal CSF. None of the patients had evidence of other neurological disorders, including previous poliomyelitis and polyneuropathies. The clinical details of the patients are listed in table 1. The diagnosis of motor neuron disease was confirmed by concentric needle electromyography showing loss of motor units, high amplitude and prolonged duration of motor unit potentials, fibrillations and fasciculations in not less than three limbs, or two limbs and the cranial musculature.

Stimulation of motor cortex and cervical region was accomplished with a Digitimer Stimulator model 180 delivering maximal electrical shocks of 750 V. Stimulus duration of 50–100 μs were used. Cortical stimulating electrodes were placed on the scalp, with the cathode on the vertex and the anode on the hand motor area of both sides (7 cm from the vertex on the line reaching the external auditory meatus). Normal controls were stimulated on one side only. Cervical electrodes were placed on the neck, the cathode over the process of T1 and the anode midline between T1 and the occiput (approximately at the level of C4 process).

Muscle action potentials evoked by stimulation of motor cortex (cortical MAPs) and cervical region (cervical MAPs) were recorded by surface electrodes placed on the biceps and thenar muscles. The EMG signals (filtered 3dB down at 50–3 kHz) were displayed and stored on a floppy disc for later analysis by an OTE Biopotential Analyzer Software Interactive System (BASIS). The cortical MAPs were collected during a slight voluntary effort. This facilitates the EMG responses.[3 8] The cervical MAPs were not influenced by voluntary muscle contraction;[3 8] therefore, the subjects

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Table 1 *Clinical features of patients*

				Upper limbs						*Lower limbs*						
				Weakness		*Tendon reflexes*		*Trophic signs*		*Weakness*		*Tendon reflexes*		*Trophic signs*		
Cases	*Sex*	*Age (yr)*	*Duration (months)*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*Bulbar involvement*
1	M	56	36	1	2	1	2	2	3	2	2	2	2	2	3	1
2	M	66	8	3	3	2	2	3	2	3	3	2	2	2	2	1
3	M	50	24	2	2	1	1	2	2	0	1	2	2	2	2	1
4	F	48	8	2	1	1	1	2	2	1	0	2	2	1	1	1
5	M	57	7	1	0	2	1	2	1	1	0	2	1	1	1	1
6	M	47	12	1	0	2	2	2	2	0	0	2	2	1	1	1
7	M	39	12	1	0	1	1	2	1	0	0	2	2	1	1	0
8	M	53	24	0	1	1	0	1	2	0	0	2	1	0	0	0
9	F	67	24	0	0	1	1	2	2	0	2	2	2	2	2	0
10	F	45	8	0	0	1	1	1	1	2	1	2	2	2	1	0
11	M	62	12	0	0	2	2	1	1	0	0	2	2	1	1	1

Weakness: 0 means absent, 1 moderate, 2 severe, 3 paralysis. Tendon reflex: 0 absent, 1 normal, 2 increased. Trophic signs: 1 normal, 2 mild hypotrophia, 3 severe hypotrophia. Bulbar involvement: 0 absent, 1 present.

were instructed to relax during cervical stimulation. The stimulation intensity was adjusted by selecting the stimulus voltage which produced the shortest response latency. Latency was measured from the stimulus artifact to the onset of the compound muscle potential. Eight to twelve responses were collected at each stimulation site and the latency of each potential was measured. The eight shortest values were used in computing the mean. Central latency was calculated by subtracting the mean latency of the cervical responses from the mean latencies of the cortical responses. The results were considered abnormal when the response was absent at maximal stimulation or their latency exceeded the upper limit of the normal range in at least one muscle. Duration was measured from the beginning to the end of the potential. Scalp and cervical stimulation were tolerated easily.

Motor conduction velocity of the median nerve was evaluated by stimulating the nerve at the elbow and wrist, and recording the muscle twitch of the abductor pollicis brevis (median nerve MAPs). Limb temperature was checked in all the subjects.

Somatosensory evoked potentials (SEPs) were recorded after stimulation of the median nerve at the wrist in 10 patients (case 5 was not studied). Five hundred square wave pulses, of 0·2 ms duration, adjusted to produce a twitch of the thumb were delivered at a frequency of 3 Hz. The SEPs were recorded from Erb's point and from the somatosensory hand area (2 cm posterior to the C3 placement of the International 10–20 System) with reference to linked mastoids. The latency of the evoked potential at the Erb's point and the latency of the first negative wave (N20) recorded from the somatosensory cortex were measured.

Results

Controls

In normal controls the stimulation of the motor cortex evoked MAPs in the biceps and thenar muscles on the opposite side (fig 1A). Similar responses at a shorter latency were obtained bilaterally after stimulation of the cervical region (fig 1b) but the potentials from the side affected by cortical stimulation were only taken into consideration.

The mean latency of the cortical and cervical stimu-

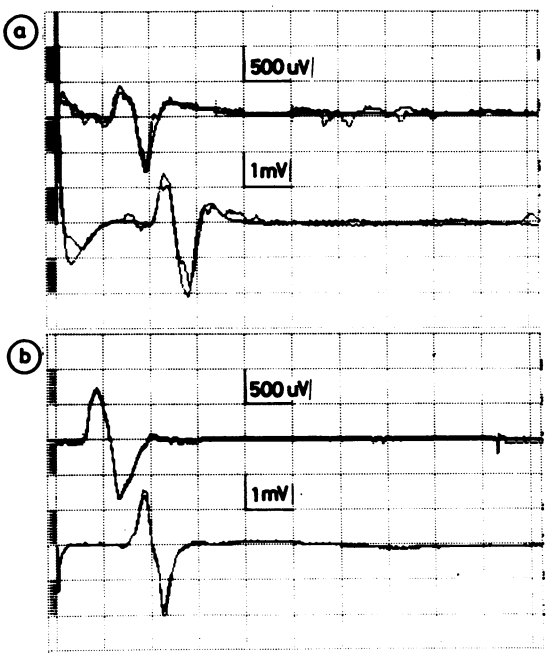

Fig 1 *Muscle action potentials in a normal subject. (a): stimulation of motor cortex; b: stimulation of cervical region. First and third trace: biceps; second and fourth trace: thenar muscles. Superimposition of two single potentials. A background EMG activity is recognisable during cortical stimulation. Horizontal calibration 10 ms/div.*

Table 2 *MAPs after cortical, spinal and peripheral stimulation*

		Cortical stimulation		Spinal stimulation				Peripheral stimulation		
		Biceps	Thenar	Biceps	Thenar	CCT		D. lat.	Amp.	MCV
Cases	Side	Latency in ms (mean ± SD)				Biceps	Thenar	ms	mV	m/s
1	R	0	0	6·0 ± 0·3	18·0 ± 0·2	/	/	5·0	1·5	45
	L	13·7 ± 1·0	25·6 ± 0·8	6·1 ± 0·7	18·1 ± 0·2	7·3	7·5	4·1	1·5	43
2	R	0	0	0	20·7 ± 0·2	/	/	5·0	0·5	31
	L	0	0	8·0 ± 0·5	16·8 ± 1·4	/	/	5·8	3·5	52
3	R	0	0	6·5 ± 0·5	0	/	/	6·0	1·5	47
	L	0	0	7·5 ± 0·5	0	/	/	6·0	1·5	41
4	R	0	0	7·5 ± 0·3	15·2 ± 0·7	/	/	3·8	3·0	44
	L	0	0	6·8 ± 0·4	15·2 ± 1·5	/	/	4·0	4·0	50
5	R	9·6 ± 1·0	18·6 ± 1·0	5·7 ± 0·5	14·9 ± 0·3	3·9	3·7	3·8	4·0	50
	L	0	21·0 ± 2·0	5·6 ± 0·4	14·6 ± 0·2	/	6·2	3·9	4·0	50
6	R	23·4 ± 3·5	31·2 ± 4·7	7·5 ± 0·6	19·0 ± 1·2	15·9	12·2	4·9	1·0	45
	L	15·2 ± 0·7	23·2 ± 1·2	6·4 ± 0·4	16·2 ± 0·4	8·8	7·0	4·3	4·0	44
7	R	12·2 ± 1·8	24·4 ± 1·7	6·6 ± 0·2	17·0 ± 0·5	5·6	7·4	3·7	2·5	47
	L	11·5 ± 0·7	22·7 ± 1·0	6·8 ± 0·5	16·8 ± 0·3	4·7	5·9	3·7	3·0	48
8	R	12·5 ± 1·6	22·1 ± 0·4	6·5 ± 0·3	17·0 ± 1·0	6·0	5·1	3·9	7·5	45
	L	10·7 ± 0·5	25·5 ± 1·2	6·5 ± 0·2	16·8 ± 1·0	4·2	8·7	3·8	9·5	45
9	R	10·5 ± 0·5	17·6 ± 0·2	6·5 ± 0·4	13·1 ± 0·6	4·0	4·5	5·0	4·4	55
	L	10·1 ± 0·4	17·7 ± 0·2	6·6 ± 0·2	12·9 ± 0·1	3·5	4·8	4·5	4·5	54
10	R	11·6 ± 2·5	17·7 ± 1·1	6·5 ± 0·3	13·1 ± 0·9	5·1	4·6	2·4	8·0	45
	L	12·3 ± 2·7	16·4 ± 0·8	6·3 ± 0·4	12·1 ± 0·4	6·0	4·3	3·0	8·0	45
11	R	10·3 ± 0·6	18·6 ± 0·7	7·2 ± 0·2	14·1 ± 0·2	3·1	4·5	3·9	9·5	53
	L	10·4 ± 0·1	19·7 ± 0·8	5·6 ± 0·1	13·6 ± 0·5	3·8	6·1	3·9	7·0	56
Mean of normal controls:		10·2 ± 1·0	19·7 ± 1·0	5·5 ± 0·8	14·3 ± 1·0	4·7 ± 0·6	5·4 ± 0·6			
Range:		9·0–12·5	17·0–22·5	5·0–7·5	13·5–17·0	4·0–5·8	5·0–6·7	2·4–4·0	4·0–10·0	45–60

CCT, central conduction time; D. lat., distal latency; amp, amplitude; MCV, motor conduction velocity.

lation MAPs and the central latency in 20 normal controls are shown in table 2. The duration of the responses was 17·0 ± 4·8 ms for the biceps and 15·0 ± 35 ms for the thenar muscles on cortical stimulation and 20·0 ± 2·2 ms for the biceps and 14·0 ± 2·2 ms for the thenar muscles on cervical stimulation.

Patients

The biceps and thenar MAPs were absent after stimulation of one hemisphere in one patient and after stimulation of both hemispheres in three patients (table 2, cases 1, 2, 3 and 4); in these patients the central latency could not be calculated. The latency of the cervical MAPs was abnormal in either the biceps or thenar muscle in the first three patients (fig 2), and within normal limits at both recording sites in case 4 (fig 3). The median nerve MAP was slightly prolonged in latency and decreased in amplitude in cases 1, 2 and 3 and within normal limits in case 4.

One patient (table 2, case 5) presented the "hemiplegic" or "Mills" variant of amyotrophic lateral sclerosis. On the most affected side the cortical MAPs were altered while the cervical and median nerve MAPs were normal. On the less affected side all potentials were normal. An increased central latency was therefore present unilaterally.

In three patients (table 2, cases 6, 7 and 8) stimulation of the motor cortex produced delayed MAPs in either the biceps or thenar muscles. Cervical MAPs were altered in the right thenar muscle in case 6 (fig 4), and within normal limits in cases 7 and 8. Central latency was prolonged. The potentials evoked by cortical stimulation were dispersed and prolonged and it was difficult to measure accurately the end of the response. Therefore the duration was not considered in computing the abnormalities. The median nerve MAP was delayed in latency and decreased in amplitude in case 6, slightly decreased in amplitude in case 7 and normal in case 8.

In three patients (table 2, cases 9, 10 and 11) the biceps and thenar MAPs on cortical and cervical stimulation were present with normal latency and duration. The median nerve MAPs were normal.

Latencies of the somatosensory evoked potentials of all patients studied were within the range of normal controls (7·0–11·0 ms at Erb's point, 17·0–21·0 ms at somatosensory cortex).

Discussion

Short and long term side effects of cortical and cervical stimulation have not been recorded so far. Single electrical shocks in the motor cortex do not provoke seizure[9] nor induce EEG changes.[10]

It is not yet established which elements of motor cortex are excited by the electrical stimulus, but the

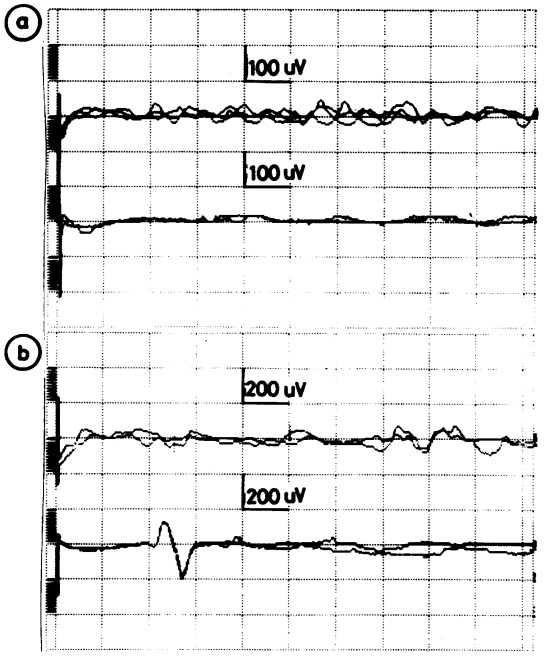

Fig 2 *Muscle action potentials in case 2. (a): stimulation of motor cortex; b: stimulation of cervical region. First and third trace: biceps; second and fourth trace: thenar muscles. The potentials are absent in both muscles after cortical stimulation, and in the biceps after cervical stimulation. The thenar potential after cervical stimulation is increased in latency and reduced in amplitude. The patient was incapable of relaxation and a slight background activity is present during cervical stimulation. Superimposition of two single traces. Horizontal calibration 10 ms/div.*

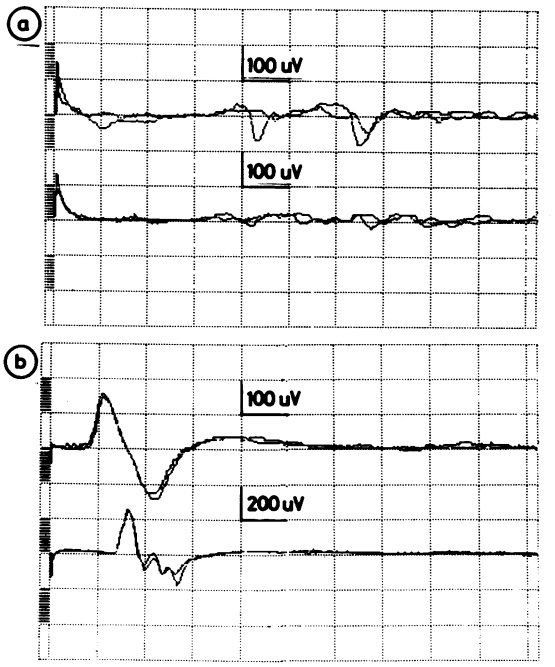

Fig 3 *Muscle action potentials in case 4. (a): stimulation of motor cortex; b: stimulation of cervical region. First and third trace: biceps; second and fourth trace: thenar muscles. The potential after cortical stimulation is unrecognisable in both muscles. Background EMG activity is recognisable during cortical stimulation. Superimposition of two single responses. Horizontal calibration 10 ms/div.*

large pyramidal neurons are the most likely.[11 12] Cervical stimulation may take place at, or close to, the motoneuron[2] but it is not clear whether the motoneurons, the interneurons or the spinal roots are stimulated. However, the finding that there were no threshold and latency differences between responses evoked in the relaxed state or during voluntary contraction suggests that the spinal roots are the site of stimulation.

Despite these uncertainties, a central latency can be calculated by subtracting the MAP latencies evoked at the two stimulation sites. Normal data are sufficiently constant to allow inferences about pathological conditions. The duration is a less reliable parameter since it is influenced by electrode position and in abnormal cases dispersion prevents accurate measurements.

In eight out of 11 patients (cases 1 to eight) with motor neuron disease we have observed absence or pathological changes of the responses evoked by cortical stimulation in at least one muscle. In four of these eight patients (cases 4, 5, 7, and 8) the responses evoked by cervical stimulation were normal, and this finding points to an alteration of the central motor pathway. In the remaining four there was also an abnormality of the MAPs evoked by cervical as well as by median nerve stimulation, a condition indicating involvement of peripheral motor pathway. However, in three of these four patients (cases 1, 2 and 3) the responses to cortical stimulation were absent, a finding surely abnormal since the response is present in all normal subjects tested in our laboratory. In the remaining one (case 6) the slowing of conduction time from cortex to muscle was out of proportion to peripheral slowing (the left cortex to thenar latency was increased by 8·7 ms while the cervical to thenar latency was only increased by 2 ms). The increased latencies of cortical MAPs were not related to difference in arm length, since the latency of the evoked potentials at Erb's point was comparable to that in normal subjects. In conclusion, in eight out of 11 patients a central abnormality can be surmised. Similar findings have been reported by Ingram and

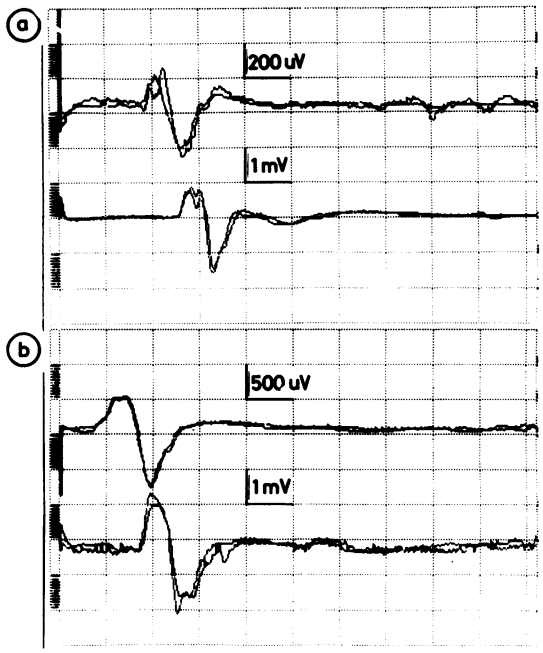

Fig 4 *Muscle action potentials in case 6. (a): stimulation of motor cortex; b: stimulation of cervical region. First and third trace: biceps; second and fourth trace: thenar muscles. The latency of the potential after cortical stimulation is increased in biceps and thenar muscles; the latency of the potential after cervical stimulation is only increased in the thenar muscles. Background activity is influenced by incomplete relaxation. Superimposition of two single responses. Horizontal calibration 10 ms/div.*

Swash[13] who found with comparable technique abnormalities in the central pathways of the brain and spinal cord.

It is well known that motor neuron disease is characterised by a variable degree of cortico-spinal tract degeneration with loss of axons and myelin sheaths and secondary glial scarring. Also there is loss of motoneuron from anterior horn gray matter. The slowing of central motor conduction is most likely related to corticospinal axon degeneration. Absence of cortical MAPs may be considered an extreme degree of this process. A similar phenomenon takes place in the peripheral nerve, where conduction slowing and temporal dispersion of impulses may account for early disappearance of tendon jerks.[14] Alternatively, it may be attributed to decreased excitability of Betz cells. The abnormalities of the cervical MAPs may be explained by loss of anterior horn cells and large myelinated fibres, and the same mechanism may account for abnormality to median nerve stimulation.[15]

The clinical correlation is not straightforward, because the motor deficit in amyotrophic lateral sclerosis results from upper and lower neuron involvement. The cortical MAPs were absent in the patients with most severe pyramidal signs, but the same patients also showed the greater degree of amyotrophy. In the patient with "hemiplegic variant" of amyotrophic lateral sclerosis (case 5) the cortical MAPs were only altered on the more affected side, but central conduction asymmetries were also present in other cases (cases 1 and 6) without clinical correlation. Also, in the single patient the degree of conduction impairment could be different in the four muscles tested. Cervical MAPs abnormality was found more often at the thenar level (cases 1, 2, 3 and 6) than at the biceps level (case 2) and this correlates with the distribution of the trophic changes.

Some investigators have recently reported alteration of somatosensory potential evoked from the lower limbs.[16,17] In our series somatosensory conduction from upper limbs were normal.

An impairment of central motor conduction is also present in patients with multiple sclerosis. In this disease the motor action potential evoked by cortical stimulation can be also absent or delayed. However, the delay is much more relevant in comparison with our findings in motor neuron disease.[4,5] A comparable behaviour is observed in peripheral demyelinating and axonal pathologies.

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